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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,294	02/17/2004	Steven W. Dow	021819-000200US	8023

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,294	DOW ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/25/04; 11/18/05; 11/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed November 10, 2006. Applicant's response to restriction requirement of September 21, 2006 has been entered. No claims were amended, cancelled or newly added. Claims 1-22 are pending in the application.

Election/Restrictions

Applicants' election for the species of "an oligonucleotide containing no CpG motifs" is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). As the requirement for restriction is deemed proper, the election requirement is maintained and hereby made Final.

Applicant timely responded to the restriction (election) requirement in the Paper filed November 10, 2006. Claims 1-22 are currently under examination.

Claim Rejections - 35 USC § 112 – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-8 and 29-31 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims embrace an enormous number of oligonucleotides lacking CpG motifs, constituting a claimed genus. The specification fails to disclose a representative number of the numerous ribonucleotides, deoxyribonucleotides or chemically modified oligonucleotides of any size or sequence composition, lacking CpG motifs, that would further be able to elicit a therapeutic systemic, non-antigen-specific immune response. The specification does not describe

the structure or functional nature of the numerous oligonucleotides, other than a single distinct sequence of a 25mer, 50mer, 75mer and a 100mer. The specification is further silent on the specific characteristics, or sequence motifs of any non-CpG oligonucleotides, that may contribute to a therapeutic immune response. The claims thus embrace a claimed genus that encompasses oligonucleotide sequences yet to be discovered.

As the specification fails to disclose any species of nematodes other than C. *elegans*, the Artisan of skill could not predict that Applicant possessed any species of said agents.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan

of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Therefore, the breadth of the claims as reading on numerous non-CpG containing oligonucleotide sequences yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the genus of oligonucleotides lacking CpG motifs. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of numerous therapeutic oligonucleotide sequences lacking a CpG motif, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112 - Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for a therapeutic composition for the elicitation of a systemic, non-antigen specific immune response in a mammal comprising a liposome delivery vehicle and an isolated oligonucleotide containing no CpG motifs, or a method of using the same, as claimed.

This rejection is based on several issues, each indicating an absence of an enabling disclosure for the eliciting a systemic immune response in a mammal, that would further be considered therapeutic, as claimed. The deficiency was identified by the Office after analysis of the disclosure provided in the instant application. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*. MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The instant specification does not provide an enabling disclosure for a composition capable of eliciting a systemic immune response in a mammal, that would further be considered therapeutic, or a method of using said composition. When given their broadest reasonable interpretation in view of the as filed specification, the claims encompass a composition comprising a liposome delivery vehicle and an oligonucleotide containing no CpG motifs, and a method for using said composition in a treatment of tumors in a mammal, when administered as a therapeutic vaccine, wherein said oligonucleotide may be either an oligodeoxynucleotide or an oligoribonucleotide, wherein the oligonucleotide may be either a phosphodiester or a phosphothioate oligonucleotide, and wherein the oligonucleotide may be of any length of size.

The specification states: "The above-mentioned method and compositions of the present invention have the advantages of eliciting a systemic, non-antigen specific immune response in a

mammal, and more particularly, of eliciting a systemic, anti-viral immune response in a mammal. Additionally, the method and composition of the present invention can elicit a systemic, anti-tumor immune response in a mammal. Such an anti-tumor immune response can result in the reduction of a tumor in the mammal." (paragraph [0015], p. 4).

Examples 12-15 of the instant specification are provided to demonstrate the potential therapeutic effects of oligonucleotides lacking CpG motifs, in eliciting a systemic, non-antigen specific immune response in a mammal. However none of the Examples are directed to assessing the effects of the oligonucleotides on reducing tumor size in a mammal. Example 12 describes the i.v. injection of oligonucleotides lacking CpG motifs, ranging in size from 10 to 100 nucleotides into mice, followed by the isolation and immunostaining of spleen cells for upregulation of CD69. The results are presented in Figure 30 and show that activation of $CD8^+/CD69^+$ cells could not be demonstrated with the 10 mer. The results further showed that while some activation of $CD8^+/CD69^+$ cells was detectable for oligonucleotides of 25 and longer lengths, the response was inferior in all cases, compared to a control 20 mer containing two CpG motifs, and contrary to the statement in paragraph [00228] of the instant specification, the responses were not as great as that elicited by the CpG containing oligonucleotide. Further, not only is there no apparent correlation between oligonucleotide size and CD69 activation (as evidenced by a decrease in activation in the 75 mer and 100 mer oligos from that seen with a 50mer), no 20 mer was included in the group of oligonucleotides lacking CpG. Thus, the differences observed between the different oligonucleotides may be due to the sequences contained therein, rather than size alone (see observations in post-filing art, below).

Example 14 describes the i.v. injection into mice of oligonucleotides lacking CpG motifs, wherein the oligonucleotides were either a 10mer or a mixture of 50mer and 75 mer, followed by the isolation and culture of spleen cells for measuring IFNγ release. While it is not clear why a mixture of two different oligonucleotides was used in the Example, or why any results from the 100mer oligonucleotide are omitted, the results showed that IFNγ release, while not detectable for the 10 mer, was present in the mixture of 50mer and 75 mer. As the positive controls in the experiment included plasmid DNA, it is not clear what conclusions may be derived by such non-

analogous comparisons. It is noted that the 20mer control oligonucleotide containing two CpG sequences, yielded very little measurable IFNγ release.

Example 15 describes the results obtained from an experiment similar to that noted in Example 14, except that IFN-α release was measured. While the 10 mer oligonucleotide did not result in any measurable IFN-α release, the mixture of 50mer and 75 mer oligonucleotides resulted in an increase in IFN-α production over that observed with the CpG oligonucleotide. However, as the oligonucleotides are of different lengths and sequences, no definitive conclusions can be drawn from the experiment. It is further noted that the results from Examples 14 and 15, depicted in Figures 32 and 33 are not directly relevant to the instant claims, as the claims are not directed to a mixture two different oligonucleotides.

Moreover, none of the examples using oligonucleotides lacking CpG motifs, included the assessment or evaluation of tumors. The specification is further silent on the sequence specific effects of the oligos, or the minimum size of an oligonucleotide required to elicit a cytokine response, or whether the cytokine release measured for some of the CpG deficient oligonucleotides would constitute a therapeutically effective amount in the treatment of a tumor.

The prior art of Auf et al. (Clin. Cancer Res. 7: 3540-3543; 2001), describes broad immunostimulatory activity by phosphorothioate oligodeoxyribonucleotides containing CpG motifs (CpG-ODNs), and induced rejection of glioma cell tumors in rats (Abstract). However, when the authors tested ODNs lacking CpG motifs, they observed, that the ODNs did not lead to significant tumor inhibition (Fig. 1, p. 3541).

The post-filing art of Vollmer et al. (Immunology 113:212-223; 2004), teaches that oligodeoxynucleotides lacking CpG dinucleotides are less potent than CpG ODN and the mechanism by which they stimulate leucocytes is not understood. Further, activation of B cells by non-CpG ODN was shown to require a new sequence motif. (Abstract). The authors further noted that the magnitude of stimulation of Toll like receptor 9 via non-CpG ODN was always inferior to that with CpG ODN, and the extent of NFκB stimulation was dependent upon the thymidine content of the non-CpG ODN (second column, p. 220). Additionally, noting: "Without a phosphorothioate backbone, the presence of CpG dinucleotides becomes more critical for immune stimulation. Only a few reports describe immune stimulation mediated by

phosphodiester non-CpG ODN, and they had usually to be added at extremely high concentrations and on several occasions." (first column, p. 221). Also observing: "non-CpG ODN induce Th2-dominated immune responses in contrast to Th1-biased effects seen with CpG ODN...as non-CpG ODN appear to lack one of the most important features of CpG ODN, the efficient stimulation of Th1-like cytokines, including type I interferons." (first column, p. 221).

A person of skill in the art would therefore have to engage in additional experimentation to develop a composition comprising any liposome and an oligonucleotide (that may further be a ribonucleotide) of any size or sequence composition that when administered to a subject, would have a therapeutic effect in reducing tumor size. Such further experimentation is regarded as undue and unpredictable, in view of the absence of sufficient guidance in either the instant specification or the prior art.

Therefore, in view of the lack of guidance provided by the specification for the therapeutic composition and a method of using the same *in vivo*, it would have required undue experimentation for one of skill in the art to practice applicant's invention as claimed. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Conclusion

Claims 1-22 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

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Fereydoun G. Sajjadi, Ph.D.
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ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

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